CMRO Current Medical Research & Opinion 3

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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To cite this article: Karen O. Klein, Ahmed M. Soliman, ElizaBeth Grubb & Paul Nisbet (2020) A survey of care pathway and health-related quality of life impact for children with central precocious puberty, Current Medical Research and Opinion, 36:3, 411-418, DOI: 10.1080/03007995.2019.1699517

To link to this article: https://doi.org/10.1080/03007995.2019.1699517

Published online: 10 Dec 2019.

CURRENT MEDICAL RESEARCH AND OPINION
2020, VOL. 36, NO. 3, 411–418
https://doi.org/10.1080/03007995.2019.1699517
Article RT-0365.R1/1699517

Taylor & Francis
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ORIGINAL ARTICLE

A survey of care pathway and health-related quality of life impact for children with central precocious puberty

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ABSTRACT

Objective: To describe the timeline to diagnosis for children with central precocious puberty (CPP) and evaluate their psychosocial and health-related quality of life (HRQoL).

Methods: A cross-sectional survey was used to prospectively collect data from caregivers, recruited *via* the MAGIC Foundation, of children with CPP. The control (non-CPP) group was recruited from a national panel of parents/caregivers. After completing a screening survey, respondents completed a burden of illness survey. Respondents in both groups completed the Pediatric Quality of Life Inventory (PedsQL) and Patient-Reported Outcomes Measurement Information System (PROMIS) peer relationship instruments.

Results: Responses from 142 caregivers of children with and 300 without CPP were assessed. Mean time to treatment after a child's visit to the pediatric endocrinologist was 220 days and time from onset of symptoms to initiating treatment was approximately 2 years. Responses to HRQoL inventories were all lower in children with CPP versus non-CPP. Adjusted mean (± standard error) PedsQL total (65.3 ± 1.8 versus 75.7 ± 1.2), Psychosocial Health Summary (62.4 ± 1.8 versus 73.4 ± 1.2), and Physical Health Summary (70.7 ± 2.2 versus 79.9 ± 1.5) scores were significantly lower ($p < .01$) in CPP versus non-CPP group. PROMIS peer relationship *T* score (± standard error) was numerically lower for the CPP versus non-CPP group (45.4 ± 1.0 versus 47.4 ± 0.7, $p = .11$).

Conclusions: In clinical practice, there is a longer than expected delay between CPP symptom onset and referral to an endocrinologist and ultimate treatment. Children with CPP experience a substantial disease burden with a significant impact on emotional, social, and physical functioning compared with children without CPP.

ARTICLE HISTORY
Received 9 July 2019
Revised 13 November 2019
Accepted 25 November 2019

KEYWORDS
Hypothalamic hormones; gonadotropin-releasing hormone; patient-centered outcomes research; physical functional performance; emotional adjustment; social adjustment; social psychology

Introduction

Central precocious puberty (CPP) is a rare disease with an incidence of 1 in 5000–10,000 children[1], characterized by early onset of puberty (before age 8 years in girls and 9 years in boys)[2] and is caused by premature activation of the hypothalamic-pituitary-gonadal axis[3]. The physical and emotional changes associated with early onset of puberty may result in psychological and social problems[4–7] and may have a substantial negative impact on health-related quality of life (HRQoL).

Treatment of CPP with a gonadotrophin-releasing hormone analogue[8] suppresses the progression of puberty, increasing adult height, and decreasing long-term psychological implications[9–12]. Early initiation of treatment improves outcomes[13,14], yet there is a paucity of data on the timing of the process from the onset of symptoms to diagnosis and eventual treatment. We sought to quantify the delay in treatment initiation and describe the journey for families from initial symptoms to seeking care and treatment. Defining the timeline to treatment stresses the importance of the primary care physician's role in evaluating children so that more optimal care can be given, and therefore better outcomes. Previous research has predominantly examined the physical outcomes of CPP, and there are few well-designed studies assessing the psychosocial impact[11]. The aim of this study was to capture information on the patient journey from the onset of CPP symptoms to diagnosis and treatment, and to evaluate the psychosocial and HRQoL burden among children with CPP in the US.

Methods

Study design

This double-blind, cross-sectional survey conducted by One Research, LLC (private research company in Charleston, SC, USA; www.oneresearchus.com), collected data prospectively from 6 April 2018 to 14 May 2018. Potential respondents were recruited by the MAGIC Foundation (Warrenville, IL,

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USA), a parent-run organization that provides support for parents/caregivers of children with CPP. The MAGIC Foundation, a non-profit organization, helps families of children diagnosed with a wide variety of growth impacting medical conditions through education, networking, physician referrals and numerous other services (www.magicfoundation.org/). Parents were invited by the MAGIC Foundation to complete a screening survey. Those who had a child with a diagnosis of CPP or with symptoms of CPP were invited to complete the main survey. The non-CPP group included 300 parents/caregivers of children without CPP who were recruited from a general population sample by One Research's partner panels; these parents/caregivers were invited by email to participate in the survey. Respondents received $30 compensation for completing the survey, which took on average 22 min to complete.

Ethical approval

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinki and consistent with International Conference on Harmonisation Good Clinical Practice and Good Epidemiology Practices. Respondents provided written informed consent prior to participation in the study. Institutional Review Board (IRB) approval was provided by the central US-approved IRB, the Copernicus Group IRB (Cary, NC, USA).

Online survey

Respondents who completed the screening survey were ≥18 years of age and resided in the US. The screening survey included age, race, comorbidities, and health care providers (HCPs).

Parents/caregivers who had a child with a diagnosis of CPP were invited to participate in the burden of illness section of the survey, which included questions regarding age the child first experienced symptoms of CPP, age they received a diagnosis of CPP, and how the diagnosis of CPP was made. The survey consisted of 54 questions collecting demographic data, data about symptoms, and treatments. Respondents were asked to select which symptoms from a list of 17 CPP-related symptoms their child experienced that made them seek medical help. They also rated how their child's symptoms changed since starting therapy using a standard, 7-point impression scale ranging from 1 (very much improved) to 7 (very much worse)[15–18]. Parents/caregivers in both the CPP and non-CPP groups completed the previously validated instruments, PedsQL and PROMIS, to obtain information on HRQoL[19–24]. Basic demographic information including marital status, employment status, education, income, and race/ethnicity was also requested.

The online survey was password protected and hosted by Survey Sampling International (SSI) on a secure server. SSI (now Dynata) is a market research and data collection company based in Shelton, Connecticut, and is one of the largest data solutions companies in the world.

HRQoL questionnaires

The PedsQL questionnaire[19] is a validated instrument used to measure HRQoL in chronically ill and healthy children[20–22]. PedsQL consists of 23 items that are used to calculate 4 subscale scores (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning), an overall Psychosocial Summary score, an overall Physical Summary score, and a Total score.

To assess the quality of the relationships children with CPP have with their friends and other acquaintances, the PROMIS parent–proxy peer relationship short-form instrument[23,24] was included as part of the online survey.

Data analysis

A convenience sample of 150 (caregivers of a child with CPP) was targeted and there were 142 respondents with a control group recruited of double that size, 300 (caregivers of a child without CPP). Data from all eligible respondents were used in the analysis. Summary descriptive statistics included mean and SD or standard error (SE) for continuous variables, and frequency and percent distributions for discrete variables. Differences in the demographic characteristics between CPP and non-CPP groups were assessed using logistic regression to create odds ratios for categorical variables and *t* tests for continuous variables. Different aspects of the care pathway were assessed, such as time to referral and diagnosis.

Each item of the PedsQL was reverse scored and linearly transformed to a scale of 0–100 with higher scores reflecting better HRQoL. Raw scores from the PROMIS instrument were translated into standardized *T* scores with a population mean of 50 and a standard deviation (SD) of 10 using the PROMIS scoring tables (Parent Proxy Version). Lower *T* scores for peer relationships indicate a worse outcome. No data imputation was performed; differences between CPP and non-CPP groups were assessed with univariate analysis of variance, adjusting for differences in demographic characteristics.

Results

A total of 142 respondents with children with CPP completed the survey; 21 boys (mean age 10.7 [0.2–18] years) and 121 girls (mean age 9.2 [0–18] years). Most respondents were white (81%) (Table 1).

CPP diagnostic path

The mean age (range) when a child first reported symptoms of CPP was 5.5 (0.1–10.5) years. In 11 children (7%, 4 boys ages 9–9.3 years, 7 girls 8–10.5 years) symptom onset was reported at >8 years old for girls or >9 years old for boys. In 89/142 (63%) of cases, the responder took their child to the physician because of symptoms they had noticed; in 23/142 (16%) cases, an HCP noted symptoms before the parent, and in 11/142 (8%) cases the child brought the symptoms to their attention. On average, medical help was sought 7.5 months after the child experienced symptoms. The most common symptoms were development of pubic hair (91/142,

Table 1. Demographics.

	CPP $N = 142$	Non-CPP $N = 300$	p Value
Children			
Age group (at time survey was conducted), *n* (%)			
<4 years	10 (7.0)	52 (17.3)	.005
5–7 years	21 (14.8)	42 (14.0)	.825
8–12 years	90 (63.4)	76 (25.3)	<.001
13–18 years	21 (14.8)	130 (43.3)	<.001
Age child first experienced symptoms of CPP, mean ± SD	5.5 ± 2.1	—	
Age child diagnosed as having CPP, mean ± SD	6.6 ± 2.2	—	
Female, *n* (%)	121 (85.2)	—	
Parents/Caregivers			
Age (year), mean ± SD	39.5 ± 6.8	38.1 ± 8.9	.100
Female, *n* (%)	133 (93.7)	222 (74.0)	<.001
Race/Ethnicity, *n* (%)			
White	115 (81.0)	220 (73.3)	.081
Hispanic	8 (5.6)	23 (7.7)	.436
Black or African American	7 (4.9)	31 (10.4)	.064
Other	12 (8.5)	26 (8.6)	.940
Marital status, *n* (%)			
Married or civil union	111 (78.2)	201 (67.0)	.017
Never married	9 (6.3)	28 (9.3)	.291
Other	22 (15.5)	71 (23.7)	.051
Employment status, *n* (%)			
Full time	65 (45.8)	162 (54.0)	.107
Part time	21 (14.8)	30 (10.0)	.143
Self-employed	12 (8.5)	12 (4.0)	.059
Other	44 (30.9)	96 (32.0)	.831
Education, *n* (%)			
Less than high school	—	1 (0.2)	
Completed some high school	3 (2.1)	6 (2.0)	.938
More than high school	139 (97.9)	293 (97.8)	.884
Household income, *n* (%)			
<$50,000	36 (25.4)	117 (39.0)	.005
$50,000–$99,999	60 (42.32)	128 (42.7)	.935
>$100,000	46 (32.4)	55 (18.3)	.001

64%) or adult body odor (68/142, 48%). In girls, the predominant symptom was development of breast buds (77%) and in boys it was development of pubic hair (81%) (Table 2).

The first HCP seen by 66% of children was a pediatrician; only 9% were first seen by a pediatric endocrinologist or an endocrinologist (8%). A total of 93 (66%) children were referred to a pediatric endocrinologist, with a mean (SE) time for referral of 143 (± 32.0) days. Following this referral, on average, children waited 59 (± 7.0) days to be seen.

The mean age (range) at diagnosis was 6.6 (0.3–11.3) years. Most children received their CPP diagnosis from a pediatric endocrinologist (93 [66%]) or endocrinologist (36 [25%]) based on bone age (118 [84%]), blood tests for hormone levels (109 [77%]), breast appearance in girls (86 [71%]), or enlargement of penis or testicles in boys (23 [57%]). Pubic hair (68 [48%]), rapid growth rate based on growth charts (57 [40%]), and risk of short adult height (25 [18%]) were also reported. Other testing included gonadotrophin-releasing hormone stimulation test (73 [51%]), magnetic resonance imaging or computed tomography scan of the head (62 [44%]), pelvic or adrenal ultrasound (38 [27%]), and genetic testing (3 [2%]). Further analysis revealed that MRI was not used for diagnosis of CPP among girls under 6 years old, 53.8% (21 of 39) and among all boys, 61.9% (13 of 21).

CPP treatment

The mean age (range) when starting treatment was 6.8 (0.8–11.5) for girls and 7.6 (2.0–10.9) for boys, with mean (SE) time to treatment after a child's visit to the pediatric endocrinologist of 220 (± 40.0) days. Overall, mean (SE) time from first symptom to treatment was 1.7 (± 0.18) years.

At the time of the survey, 86 (61%) children were receiving treatment, 32 (22%) had received treatment in the past, and 21 (17%) had never received treatment. Forty-seven (40%) patients received only depot leuprolide acetate, 45 (38%) received only histrelin acetate and 15 (13%) received both treatments. The primary reason for using leuprolide was preference by the physician (22 [36%]) or not wanting the child to undergo a surgical procedure (11 [18%]), whereas the primary reason for using histrelin was so the child did not have to think about treatment all year (21 [35%]) or because the child was afraid of injections (12 [20%]).

CPP treatment evaluation

Pubertal suppression was assessed by bone age ($n = 85$, 72%), growth rate ($n = 78$, 66%) and changes in pubertal Tanner staging[25] ($n = 73$, 62%). Changes in luteinizing hormone levels were most commonly measured once every 6 months ($n = 39$, 49%) or once every 3 months ($n = 23$, 29%).

Of patients ever treated ($n = 110$), the main treatment-related concerns were side effects (short term: $n = 82$, 75%; long term: $n = 28$, 26%) and impact on emotional/mental state ($n = 16$, 15%). Approximately one-third (31%) of children changed or switched their initial treatment, stating the treatment was not working well enough ($n = 10$, 27%), child

Table 2. Major symptoms experience prior to diagnosis.

Major symptoms experienced[a]	Male, % ($n = 21$)	Female, % ($n = 121$)	Total n (%)
Development of breast buds	*n/a*	76.9	93 (–)
Development of pubic hair	81.0	61.2	91 (64.1)
Adult body odor	38.1	48.8	68 (47.9)
Mood or emotional changes	42.9	44.6	63 (44.4)
Growth spurt	38.1	43.8	61 (43.0)
Changes in body growth	14.3	27.3	36 (25.4)
Development of body hair under arms	23.8	22.3	32 (22.5)
Vaginal discharge	*n/a*	20.7	25 (–)
Acne	33.3	16.5	27 (19.0)
Development of whole body hair	23.8	10.7	18 (12.7)
Onset of menstruation (periods/vaginal bleeding)	*n/a*	9.9	12 (–)
Development of facial hair	33.3	0.8	8 (5.6)
Testicle enlargement	33.3	*n/a*	7 (–)
Penis enlargement	23.8	*n/a*	5 (–)
Interest in sexual behavior or ideas	4.8	2.5	4 (2.8)
Other	4.8	2.5	4 (2.8)
Sexual behaviors	4.8	0.1	2 (1.4)

[a]Respondents were asked to select all that applied, therefore sums >142 and >100%.

was afraid of injections ($n = 6$, 16%), or HCP preference ($n = 6$, 16%).

Most children visited the physician managing their CPP once every 3 months ($n = 50$, 35%) or once every 6 months ($n = 44$, 31%).

Of the predominant symptoms that led to the parent to seek medical help, 16% ($n = 76$) reported much or very much improvement in the amount of pubic hair and 17% ($n = 58$) reported an improvement in body odor following initiation of therapy.

Impact on HRQoL

Responses from 142 parents/caregivers in the CPP group and 300 parents/caregivers in the non-CPP group were evaluated to assess the impact of CPP on HRQoL. The average age of the parent/caregiver and the employment status were similar in the CPP versus non-CPP group (Table 1). Most respondents were women (94% and 74%, respectively). Significant differences in demographic characteristics included age group at the time the survey was conducted, sex of the parent/caregiver, martial status, and household income (Table 1).

Unadjusted mean PedsQL scores are provided in Table 3. Based on the univariate analysis of variance, adjustments were made for differences in demographic characteristics (Figure 1). Adjusted mean (±SE) PedsQL total (65.3 ± 1.8 vs 75.7 ± 1.2), Psychosocial Health Summary (62.4 ± 1.8 vs 73.4 ± 1.2), and Physical Health Summary (70.7 ± 2.2 vs 79.9 ± 1.5) scores demonstrated significantly lower ($p < .01$) HRQoL for the CPP group compared with the non-CPP group. PedsQL subscale scores ranged from 57.6 to 70.7 in the CPP group and from 69.8 to 79.9 in the non-CPP group; in both groups, the lowest scores were reported for emotional functioning, and the highest scores for physical functioning; all values were significantly lower ($p < .01$) for the CPP group than for the non-CPP group (Figure 1). PedsQL scores did not differ between children currently receiving treatment and those treated in the past. These scores also did not differ for children with CPP who were never treated compared with those who received treatment.

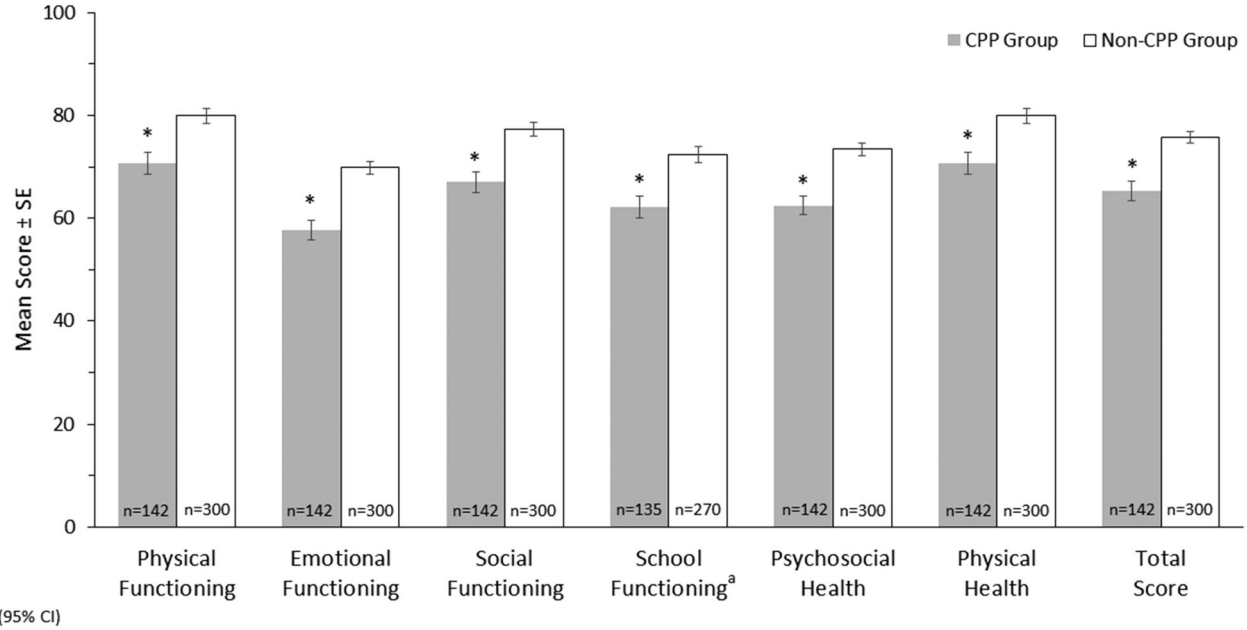
Table 3. Parent/Caregiver-reported PedsQL and PROMIS peer relationship T scores: unadjusted analysis.

Measure (mean ± SE)	CPP $N = 142$	Non-CPP $N = 300$	p Value
PedsQL total score	65.6 ± 1.6	75.6 ± 1.2	<.05
Physical health summary	71.8 ± 2.2	79.4 ± 1.4	<.05
Psychosocial summary	62.2 ± 1.5	73.5 ± 1.2	<.05
Physical functioning	71.8 ± 2.2	79.4 ± 1.4	<.05
Emotional functioning	56.7 ± 1.6	70.3 ± 1.2	<.05
Social functioning	67.0 ± 2.1	77.3 ± 1.3	<.05
School functioning[a]	62.7 ± 2.0	72.2 ± 1.4	<.05
PROMIS T score	45.2 ± 1.0	47.5 ± 0.7	<.05

[a]Seven children in the CPP group and 30 children in the non-CPP group (all ≤4 years of age) were excluded because they were not enrolled in school/daycare.

The greatest impact was seen on emotional functioning where scores were significantly lower ($p < .001$) by at least 13 points in the CPP group versus non-CPP group for all five items. Compared with the non-CPP group, parents/caregivers in the CPP group reported that their child had more problems feeling afraid or scared, sad or blue, or angry, had more trouble sleeping and were more worried about what would happen to themselves. They also reported more teasing and trouble completing tasks or forgetting things. Children with CPP reported more hurts and aches, lower energy level, and less participation in sports.

The adjusted PROMIS peer relationship T score (±SE) was lower in the CPP group compared with the non-CPP group (45.4 ± 1.0 vs 47.4 ± 0.7, $p = .11$, unadjusted T scores are provided in Table 3). Fewer parents/caregivers in the CPP group (range: 55–62%) responded 'often' and 'almost always' to statements describing positive interactions of their child with other children compared with those in the non-CPP group (range: 73–78%). For example, 76% of parents in non-CPP group reported that their child was good at making friends versus 57% in the CPP group (Table 4). More parents in the non-CPP versus the CPP group reported that other children wanted to talk to their child (76% vs 56%) and be their child's friend (74% vs 55%).



Mean (95% CI)

CPP	70.7 (66.3–75.0)	57.6 (53.8–61.3)	67.0 (62.9–71.2)	62.2 (57.9–66.5)	62.4 (59.0–65.9)	70.7 (66.3–75.0)	65.3 (61.8–68.9)
Non-CPP	79.9 (77.0–82.8)	69.8 (67.3–72.3)	77.3 (74.6–80.0)	72.4 (69.5–75.3)	73.4 (71.2–75.7)	79.7 (77.0–82.8)	75.7 (73.4–78.1)

Figure 1. Parent/caregiver-reported PedsQL scores. Differences between CPP and non-CPP groups were assessed using analysis of variance, adjusting for differences in demographic characteristics (age group at time survey was conducted, sex of the parent/caregiver, marital status, and household income). The asterisk (*) denotes $p < .01$ for difference in adjusted mean score between the CPP and non-CPP groups. [a]Seven children in the CPP group and 30 children in the non-CPP group (all ≤4 years of age) were excluded because they were not enrolled in school/daycare. Abbreviations. CI, Confidence interval; SE, Standard error.

Table 4. Parent/caregiver responses for the individual items of the PROMIS peer relationship instrument.

Responses, *n* (%)	CPP					Non-CPP				
	Never	Almost never	Sometimes	Often	Almost always	Never	Almost never	Sometimes	Often	Almost always
(1) My child felt accepted by other children his/her age	3 (2)	7 (5)	44 (31)	34 (24)	54 (38)	16 (5)	10 (3)	40 (13)	93 (31)	141 (47)
(2) My child was able to count on his/her friends	3 (2)	17 (12)	38 (27)	37 (26)	47 (33)	13 (4)	11 (4)	57 (19)	105 (35)	114 (38)
(3) My child was good at making friends	4 (3)	25 (18)	32 (23)	29 (20)	52 (37)	8 (3)	21 (7)	43 (14)	91 (30)	137 (46)
(4) My child and his/her friends helped each other out	3 (2)	15 (11)	40 (28)	37 (26)	47 (33)	9 (3)	15 (5)	54 (18)	104 (35)	118 (39)
(5) Other children wanted to be my child's friend	2 (1)	12 (8)	50 (35)	27 (19)	51 (36)	9 (3)	11 (4)	59 (20)	95 (32)	126 (42)
(6) Other children wanted to be with my child	2 (1)	13 (9)	47 (33)	32 (23)	48 (34)	10 (3)	7 (2)	56 (19)	104 (35)	123 (41)
(7) Other children wanted to talk to my child	1 (1)	13 (9)	48 (34)	29 (20)	51 (36)	9 (3)	8 (3)	57 (19)	95 (32)	131 (44)

Significantly more parents/caregivers in the CPP group versus non-CPP group reported that their child received a diagnosis of migraines (8.5% vs 1.3%, $p < .001$; Table 5). Although not statistically significant, parents/caregivers reported that 13.4% of children with CPP received a diagnosis of anxiety since the diagnosis of CPP was made, compared with 11.0% in the non-CPP group.

Table 5. Comorbid conditions.

Condition[a], *n* (%)	CPP[b] *N* = 142	Non-CPP *N* = 300	*p* Value
Anxiety	19 (13.4)	33 (11.0)	.468
Migraines	12 (8.5)	4 (1.3)	<.001
Eczema	10 (7.0)	40 (13.3)	.051
Depression	7 (4.9)	14 (4.7)	.903
Lactose intolerance	6 (4.2)	11 (3.7)	.775
Anemia	6 (4.2)	11 (3.7)	.775
Asthma	5 (3.5)	40 (13.3)	.001
Non-specific allergy	3 (2.1)	24 (8.0)	.016
GERD	3 (2.1)	4 (1.3)	.540
IBS	0	8 (2.7)	.050
Wheat allergy	1 (0.7)	6 (2.0)	.308
None of these	92 (64.8)	168 (56.0)	.080

[a]Conditions with <2% prevalence in both groups are not shown.
[b]Comorbid conditions diagnosed since CPP diagnosis.
Abbreviations. GERD, Gastroesophageal reflux disease; IBS, Irritable bowel syndrome.

Discussion

This study, the first of its kind to be conducted in a relatively large sample size among children with CPP in the US, sought to characterize the patient journey from the onset of CPP symptoms to diagnosis, and evaluated the psychosocial burden and HRQoL in these children and their parents/caregivers. The online survey design provides much-needed insights into the real-world experience of CPP and natural history of CPP (including symptoms, diagnosis, and treatment).

Results from this study demonstrate that on average across the US, the time from symptom onset to treatment is almost 2 years. Survey responses also demonstrated that some children, although diagnosed with CPP, never

received treatment. An unexpected finding was that only 18% of caregivers were concerned about short adult height. It is also interesting that 11 children with early, but normal onset puberty, were treated for concerns that puberty was precocious. Caution is needed in interpreting this result, since it is based on caregiver recall. This highlights another need for the development of additional educational resources related to the challenge of distinguishing CPP from early normal variant puberty[2]. The average age for onset of puberty is decreasing for both girls and boys[26], with socio-economic conditions influencing age at onset as well as large variations between ethnic groups, contributing to the challenge of distinguishing between precocious and normal puberty[27].

Delays introduced by parents/caregivers between symptom onset and visiting an HCP may also be markedly reduced by more widespread education highlighting that although rare, the symptoms of this disease should not be ignored. This study also demonstrates an even split between two of the most used treatment options to date, leuprolide acetate and histrelin acetate. This emphasizes the need for individualized treatment options, as physicians, parents, and patient concerns are not all similar.

The current standard of care for the evaluation of CPP includes at minimum: measurement of hormone levels, bone age x-rays, documentation of breasts in girls, or increases in testicular size in boys. Interestingly, this study based on caregiver recall, did not demonstrate that all those things were assessed. The fact that these measures were not performed may be partially a result of weakness in recall, but also reflects different provider practices. Performance of magnetic resonance imaging scan of the head is still debated in children older than 6 years of age, and is a measure that caregivers are more likely to remember; therefore, it is relevant that not quite half of the children had a magnetic resonance imaging scan done. These findings highlight a considerable variability in practice across the US and further emphasizes the need for physician and caregiver education.

Because CPP is a rare disease, the number of published studies examining CPP is limited and most studies have small sample sizes[7,9,28–35]. However, a longitudinal study performed by Mensah et al.[35] examined psychosocial adjustment in a large sample of Australian children using PedsQL. The Mensah study found that children who experienced early puberty (by 8–9 years) had poorer Psychosocial Health Summary scores across childhood than those who did not. The lowest PedsQL sub-scores in that study were reported for emotional functioning, although lower scores were also reported for all other PedsQL sub-scores[35].

Our results are consistent with those in the Mensah study[35] and show that children with CPP have more unfavorable PedsQL summary scores than children without CPP. The impact compared with children without CPP was greater on psychosocial health than on physical health with the biggest difference seen in emotional functioning and included problems of feeling afraid or scared, sad or blue, and angry as well as trouble sleeping and being worried about what would happen to themselves. It is understandable that children going for frequent medical appointments would wonder more about their health. Peer relationships may also contribute to their emotional functioning. They reported more teasing, which may be related to tall stature and early physical changes. The report of increased trouble completing tasks or forgetting things is not easy to understand, and further study is needed. Children with CPP reported more hurts and aches, which is understandable since they were undergoing injections and blood tests. Lower energy level and less participation in sports is not expected as found, unless it is related to the emotional issues described.

Children treated for CPP did not have better scores than those children with CPP who did not receive treatment. However, several of the weaknesses of this study may have influenced that result. The age of onset of puberty and specifics of treatment are based on parent recall and in some cases over many years. Additionally, the study was not designed to compare results before and after treatment, which is an important area of interest for future study. Also, some children had earlier onset of normal puberty and the rate of progression of puberty is not defined. There were not enough children between 8 and 10 years of age at reported onset of pubertal symptoms to compare their results to the children with true CPP.

Peer relationships play an important role in social development[36–38]. The PROMIS peer relationship scores (a measure of social development) for the CPP group were below those of the non-CPP group and were also below the population mean of 50[39,40]. Parent/caregiver responses indicated that children with CPP have more problems being accepted by other children their age and making friends. Thus, results using two separate instruments demonstrate a significant negative effect of CPP on psychosocial health in children with CPP.

Further study is needed to determine whether treatment improves psychosocial outcomes. In the meantime, these results emphasize the need for appropriate medical treatment to ease the burden for children suffering from CPP.

There are several limitations to this study which should be noted. The length of the survey might have contributed to the quality of parents' responses to the survey questions. Information from respondents who answered 'never received treatment' was not captured and would have provided useful information on why treatment was not initiated. Furthermore, diagnosis was self-reported and not clinically verified. Recall bias, a limitation common to studies of this nature, and sample selection bias may have been introduced. Because responses were collected from parents who are members of the MAGIC Foundation, they may not be completely generalizable to the entire CPP population. However, one would suspect that parents involved in this group would be more attentive and thus the true delay in onset of treatment may be even greater. Bias due to unobservable covariates cannot be completely ruled out. In addition, the data rely on the opinions of the caregivers. Another limitation is that the study included both children with CPP and a few children with early puberty who were treated (8–10-year-old girls). The nature of the survey makes it impossible to know whether the children actually had the onset of puberty prior

to age 8 years, whether the parents did not recall, or whether there was a reason a physician chose to treat someone in that early normal pubertal age range. Finally, this analysis was performed on a population that included patients who were currently being treated, those who had been treated in the past but were not currently being treated, as well as those who never received any treatment. Further study is needed as we would expect appropriate treatment to improve HRQoL. Awareness of these issues highlights the importance of further study regarding the relationship of treatment to changes in HRQoL.

Conclusions

Findings from this caregiver survey suggest that there exists, on average, a marked delay between CPP symptom onset, referral to an endocrinologist, and ultimately treatment for this rare disease. Furthermore, children with CPP experience a substantial disease burden with a significant negative impact on HRQoL including emotional, social, and physical functioning compared with children without CPP. Minimizing the time from onset of symptoms to treatment should have a positive impact on HRQoL in both patients and parents/caregivers, as well as treatment outcomes.

Transparency

Declaration of funding

All funding for this study was provided by AbbVie. AbbVie personnel participated in the analysis and interpretation of data, drafting, reviewing, and approving the publication. All authors contributed to the development of the publication and maintained control over the final content.

Declaration of financial/other interests

AMS and EG are AbbVie Inc. employees and may own AbbVie Inc. stocks/stock options. PN has no competing interests relevant to this manuscript. KOK has been a consultant for AbbVie Inc. but was not paid for any part of this manuscript preparation. AbbVie personnel participated in the analysis and interpretation of data, drafting, reviewing, and approving the publication. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved the submission.

Acknowledgements

The authors would like to thank the MAGIC Foundation for their participation in the study. Medical writing assistance was provided by Fiona Woodward, PhD, and Joann Hettasch, PhD, of JK Associates, Inc (a member of the Fishawack Group of Companies). These services were paid for by AbbVie.

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